Medical Tribune

and Medical News

Vol. 16, No. 2 — world news of medicine and its practice—fast, accurate, complete — Wednesday, January 15, 1975

making rounds at press time

EVISED REPORT on X-ray xposures, to be published n the Bureau of Radiologi- al Health Bulletin in ebruary or March, will how more than 50 per cent eduction in prior esti- ates of "gonadal and entically significant" er exposure levels, ding to John C. orth, bureau director. e estimates of 55 milli- ads in 1964 and 36 in 1970 ere based on errors in ose model and computer rogram, he said.

OSTON HOSPITAL MERGER ree major Harvard teach- hospitals have merged one hospital corpora- n to be known as ffiliated Hospitals enter. Merging are Boston ospital for Women, Peter ent and Robert B. Brigham spitals. New center, to be built on parking lot djacent to PBB, will have 640 acute beds, 40 skilled nursing and rehab beds.

INFLUENZA DEATHS may rise to an "order of magnitude" of 200-400 excess cases per week this winter, according to the Center for Disease Control. This tentative prediction is based on confirmed outbreaks in Georgia, western Tennessee, northern Michigan and eastern New York. Dr. Charles Hoke, CDC Medical Epidemiologist, said the disease incidence is still "geographically sporadic", but if the disease pattern follows that of the epidemic winter, 1971-72, weekly deaths could go into the excess-of-400 range for 6 to 8 weeks.

RETIRING TO N. CAROLINA -- Dr. Adrian H. Scolten of Portland, Me., who once ran against Margaret Chase Smith for U.S. Senator, and was an early advocate of 50-mph speed limit. He is now 83

Massive Glucose Shown Lifesaving in Shock

By NATHAN HORWITZ

Medical Tribune Staff

DALLAS—Massive infusions of glucose have consistently prevented death from endotoxin shock in a series of experimental studies, the American Heart Association was told here.

In what is believed to be the first demonstration of the lifesaving efficacy of glucose in shock, a University of Oklahoma team reported that in two series of controlled studies, dogs that received continuous glucose infusions after intravenous administration of lethal doses of E.coli endotoxin "all survived," while most untreated animals died.

Even when glucose infusions were started after the animals became severely hypoglycemic, the treated group survived, "but no animal survived that did not receive exogenous glucose," said Leonard B. Hinshaw, Ph.D., Research Professor of Surgery and Professor of Physiology and Biophysics.

In detailing the findings, Dr. Hinshaw said the glucose studies were started following his team's unexpected observation that hypoglycemia developed in most animals during the later stages of endotoxin shock.

"In all experimental shock studies hitherto, all of the animals died. We asked ourselves what would happen if we simply infused glucose during the shock state and gave just enough to keep up with the animal's requirements," Dr. Hinshaw related.

Thirty-five anesthetized animals received I.V. infusions of E.coli endotoxin (1.0-1.5 mg./kg.). The animals were evaluated for an initial five-hour period and all survivors were observed

Continued on page 12

Resignations Renew Call for Fed. Health Dept.

Medical Tribune Staff

WASHINGTON—The resignation of two of the nation's top health officials within one week has brought renewed calls for an independent federal Department of Health and an end to the "politicization of science."

The demands came from Nobelists, lawmakers and medical leaders after Drs. Charles C. Edwards, Assistant Secretary of Health and Robert S. Stone, Director of the National Institutes of Health, announced here that they were leaving their posts. Dr. Stone's resignation is the second from the NIH top spot in 18 months.

"The turnstyle tenure of those in top positions in the nation's health programs emphasizes the need for a separate National Department of Health, independent of the Department of Health, Education and Wel-

Continued on page 35

10-20-Year Pacemaker

A new, smaller pacemaker, rechargeable from the outside of the body for 10 to 20 years, has been developed at Johns Hopkins University. Here, four-year-old Jennifer ... gets her pacemaker recharged by her mother.

Controversy Continuing Over XYY Screening

Medical Tribune Report

BOSTON—Despite a Harvard Medical School committee's conclusion that a program screening newborn boys for chromosome abnormalities should be continued, criticism of the ethics and good scientific practice of the project has not let up.

Critics of the project called the recommendation from the Standing Com-

Continued on page 6

Adriamycin Combination Gets 55% Sarcoma Response Rate

BY FRANCES GOODNIGHT

Medical Tribune Staff

HOUSTON—"Encouraging results" in patients who have metastatic soft-tissue and bony sarcomas are being achieved by treatment with adriamycin in combination with other anticancer drugs, Dr. Jeffrey A. Gottlieb reported here.

Dr. Gottlieb, chief of the chemotherapy service at the University of Texas M.D. Anderson Hospital and Tumor Institute, said that the most successful combination tried so far at his center, in collaboration with other institutions of the Southwest Oncology Group, has been adriamycin, cyclophosphamide, imidazole carboxamide (DIC), and vincristine.

This four-drug regimen produced an over-all response rate of 55 per cent in 136 patients having various types of sarcoma, the investigator told a clinical conference sponsored by Anderson Hospital and the American Cancer Society. Complete remissions occurred in 14 per cent.

By comparison, the over-all response rate for adriamycin alone has been 31 per cent, while adriamycin-DIC and adriamycin-DIC-vincristine each yielded an over-all response rate of 42 per cent, with complete response rates of 11 per cent and 9 per cent respectively.

Survival times have also improved

Continued on page 29

Serum-Lipids Mass Screening Test Devised

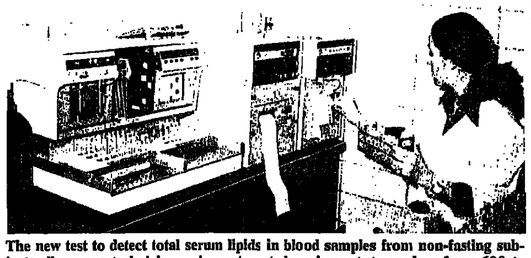
Medical Tribune Report

DALLAS—A simple, rapid and inexpensive mass screening test to detect total serum lipids in casual samples of blood from non-fasting subjects has been developed by teams of investigators at Rockefeller University and Albert Einstein College of Medicine, New York.

The test, based on a simplified version of the heparin precipitation method, has proved reliable in primary screening of 126,085 apparently healthy subjects, according to Dr. William Insull, Jr., associate director of the Center for Prevention of Premature Atherosclerosis, Rockefeller University.

The procedure's simplicity is such that one technician, using automated equipment, can analyze from 600 to 1,200 samples a day, employing reagents costing less than one cent per test, Dr. Insull told the annual meeting of the American Heart Association. A single technician, he reported, was responsible for analyzing the entire series of more than 126,000 subjects in the first year and identifying 6,117 persons with high serum lipoprotein levels.

Followup examination of the high-lipid subjects by traditional methods, the investigator said, showed that 10 per cent had hypercholesterolemia, 36 per cent hypertriglyceridemia, and 26 per cent hyperlipidemia. Twenty-seven per cent had serum lipids within normal limits, defined as cholesterol and triglyceride levels within the limits seen in all except the upper five percentiles of the population.



The new test to detect total serum lipids in blood samples from non-fasting subjects allows one technician, using automated equipment, to analyze from 600 to 1,200 samples a day, employing reagents costing less than 1 cent per test.

Turbidity Readily Assayed

The heparin turbidity test, developed by the Einstein group, measures the lipid suspension formed by the reaction of serum lipoproteins to heparin and calcium chloride. The degree of turbidity is proportional to the level of lipoproteins and is readily assayed by a spectrophotometer. The test was developed by Drs. Meyer Burstein, Howard A. Eder and Harold R. Scholnick of Albert Einstein. The latter two also collaborated in the screening study of the simplified version of the method.

Dr. Insull commented that the new test offers results "comparable to those obtained for other populations using traditional methods."

"This test makes practical the routine and inexpensive screening of large numbers of apparently healthy subjects to detect those with high serum lipid levels and an increased risk of coronary heart disease—persons for whom treatment may be instituted before clinical disease develops."

Other collaborators were Dr. Robert L. Hirsch of the New York Blood Center, and Elaine Barzellator of Rockefeller University. N.H.

Leukemia Therapy Unneeded After 3 Years

Medical Tribune Report

SAN FRANCISCO—Continuance of maintenance therapy after three years in children who have had acute leukemia does not appear to affect the status of the patients, a Minnesota study has shown.

Dr. Mark Nesbit of the University of Minnesota Hospitals reported here on a small series in which six of eight patients first treated in 1967, but receiving no maintenance therapy after three years, are still alive and well, while four of seven patients who received continued therapy are still alive.

Dr. Nesbit noted that despite extended survivals, leukemia is not "cured." Leukemia can only be considered "cured" when the survival rate for leukemia patients is parallel to the normal survival rate, he said.

He told members of the American Academy of Pediatrics meeting here that physicians miss the diagnosis in 10-15 per cent of leukemic children.

Great Variations

Also, he continued, 10 to 15 per cent of all leukemia cases are a morphological type resistant to therapy, 10 to 15 per cent of the children will die of drug induced or treatment-induced toxicity, and 50 per cent will survive for five years with some small percentage of those "cured."

He suggested that the great variations are due to the fact that leukemia is not a single disease but a number of morphologically different diseases. It is important to distinguish among these, he reminded, to give the best possible therapy.

Reliable diagnosis can not be made on the basis of the initial white count, since 75 per cent of the children will have a white count below 20,000, he said.

The physician should be alert to other signs and symptoms, such as headache and bone pain, he cautioned. In fact, all children with a diagnosis of rheumatoid arthritis should have a bone marrow aspiration to be sure the pain is not due to leukemia.

In terms of treatment, he continued, prednisone, vincristine and L-asparaginase give a high remission rate in acute lymphoblastic leukemia, but have no effect in acute myelogenous leukemia.

Daunorubicin and cytosine arabinoside, he said, give a similar remission rate in both types.

The greatest problem in the 50 per cent who do not survive five years, Dr. Nesbit observed, is neurological involvement secondary to acute leukemia, and pre-treatment for this complication is indicated.

Dr. Nesbit cautioned that complications arising from drug therapy for leukemia can at times be more life-threatening than the disease itself.

As an example he noted that methotrexate, "the mainstay of maintenance," is associated with hepatic fibrosis and pulmonary disorders, as well as gastrointestinal ulceration. Early hepatic changes are reversible, but chronic changes which can occur after two years, are irreversible. Pulmonary disease in which the Pneumocystis organism is involved is life threatening, he said, with patient mortality 50 per cent even with treatment.

Drug therapy should be discontinued when there is evidence of serious or immunologic impairment, or when it is no longer necessary, he said.

In a related presentation, Dr. Barbara Jones of the West Virginia University School of Medicine attributed increased survival in childhood leukemia to the availability of new drugs, the use of combinations of drugs, and to early treatment of the central nervous system.

Meningeal Leukemia Up

With increasing survival, the incidence of meningeal leukemia has increased to 50 or 60 per cent, she observed, a finding which suggests that small numbers of leukemic cells are present in the central nervous system from the beginning.

Prophylactic therapy with a combination of intrathecal methotrexate and cranial radiation, or with craniospinal radiation alone, appears to significantly reduce the relapses due to central nervous system involvement, she said.

CNS treatment is toxic, Dr. Jones acknowledged, noting, however that "the overall toxicity is not severe enough to outweigh its marked advantage."

ECTOPIC BEAT

The A.M.A. in *American Medical News*, announced "six new, exciting A.M.A. educational opportunities in six fantastic settings!" The fifth on was listed as **"Peru-Chili-Brazil,"** and that's what we call a *really* fantastic setting. If a little on the hot side.

(Regular beat: Intensive Medics, page 39.)

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CLINICAL NEWS NOTE: *"Right now, it's almost as if anyone wanting to do an investigation automatically must be thought to be unethical, and from that point on he must prove himself ethical." (Dr. Stanley Walzer, see pg. 6.)*

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reserpine 0.1 mg
hydralazine hydrochloride 25 mg
hydrochlorothiazide 15 mg

INDICATIONS
Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications as follows:
Effective: Hypertension. (See box warning.)

WARNING
This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

CONTRAINDICATIONS
Reserpine: Known hypersensitivity; mental depression (especially with suicidal tendencies); active peptic ulcer; ulcerative colitis; electroconvulsive therapy.
Hydralazine: Hypersensitivity; coronary artery disease; mitral valvular rheumatic heart disease.
Hydrochlorothiazide: Anuria; hypersensitivity to this or other sulfonamide-derived drugs. The routine use of diuretics in an otherwise healthy pregnant woman with or without mild edema is contraindicated and possibly hazardous.

WARNINGS
Reserpine: Use with extreme caution in patients with a history of mental depression. Discontinue at first sign of despondency, early morning insomnia, loss of appetite, impotence, or self-deprecation. Drug-induced depression may persist for several months after drug withdrawal and may be severe enough to result in suicide. MAO inhibitors should be avoided or used with extreme caution.
Hydralazine: Chronic administration of doses over 400 mg daily may produce an arthritis-like syndrome simulating acute systemic lupus erythematosus. This may also occur at lower doses. Long-term treatment with steroids may be necessary and relapse have been detected many years later. CBC's, L.E. cell preparations, and antinuclear antibody titer determinations are indicated before and periodically during prolonged therapy with hydralazine or if the patient develops any unexplained signs or symptoms.
Use MAO inhibitors with caution.
Hydrochlorothiazide: Use with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.
Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte imbalance may precipitate hepatic coma.
Thiazides may be additive or potentiative of the action of other antihypertensive drugs. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs.
Sensitivity reactions are more likely to occur in patients with a history of allergy or bronchial asthma.
The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Usage in Pregnancy
Reserpine: The safety of reserpine for use during pregnancy or lactation has not been established; therefore, the drug should be used in pregnant patients or women of childbearing potential only when, in the judgment of the physician, it is essential to the welfare of the patient. Increased respiratory tract secretions, nasal congestion, cyanosis, and anorexia may occur in neonates and breast-fed infants of reserpine-treated mothers since reserpine crosses the placental barrier and appears in maternal breast milk.
Hydralazine: The drug should be used only when, in the judgment of the physician, it is deemed essential to the welfare of the patient.
Hydrochlorothiazide: Usage of thiazides in women of childbearing age requires that the potential benefits of the drug be weighed against its possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

Nursing Mothers
Thiazides cross the placental barrier and appear in cord blood and breast milk.

PRECAUTIONS
Reserpine: Use cautiously in patients with history of peptic ulcer, ulcerative colitis, or gallstones (biliary colic may be precipitated).
Exercise caution when treating hypertensives with renal insufficiency. Use cautiously with digitalis and quinidine.
Intraoperative hypotension has occurred in hypertensive patients receiving rauwolfia preparations, but withdrawal of reserpine does not assure that circulatory instability will not occur in such patients.
Hydralazine: Use cautiously in suspected coronary artery or other cardiovascular disease, cerebral vascular accidents, and advanced renal damage. Postural hypotension may occur, and the pressor response to epinephrine may be reduced.

In treating hypertension, current clinical practice stresses the importance of achieving control of three basic homeostatic mechanisms: fluid volume, sympathetic activity, and arteriolar tone.[1]

Initial treatment most frequently employs one of the thiazides.[2-7]

But if blood pressure resists fluid volume control with thiazides, a second agent with a different mode of action, such as a sympathetic inhibitor (reserpine), may be gradually added.[2-4]

Many hypertensives, however, may resist control even with a two-drug regimen.

In such cases, the crucial "third step" in combined therapy is frequently control of arteriolar tone with hydralazine.[2-4]

Ser-Ap-Es combines all three steps in a single tablet—all the medication many hypertensives will need.

And when the dosage of each component corresponds to the dosages pre-established by individualized titration, Ser-Ap-Es may prove more convenient and more economical.

Doses of each component in Ser-Ap-Es are lower than when used alone.

Note: Use Ser-Ap-Es cautiously in patients with advanced renal damage or cerebrovascular accident. Discontinue at first sign of mental depression.

Ser-Ap-Es is the only antihypertensive agent that provides the three basic drugs used in two published VA cooperative studies.[8,9]

References: 1. Freis ED: Hypertension: a controllable disease. *Clin Pharmacol Ther* 13:627-632, 1972. 2. Even a little is too much. *Emergency Med* 5:144-185, 1973. 3. Bender AD: Familiar Rx: Combination drug therapy in hypertension. *Del Med J* 40:5-8, 1968. 4. Bourne HR, Melmon KL: Guides to the pharmacologic management of essential hypertension. *Ration Drug Ther* 5:1-7, 1971. 5. Russell RP: Hypertension, in Harvey AM, Johns RJ, Owens AH, et al (eds): *The Principles and Practice of Medicine*, ed 18. New York, Appleton-Century-Crofts, 1972, pp 331-334. 6. Gifford RW Jr: Drugs for arterial hypertension, in Modell W (ed): *Drugs of Choice, 1972-1973*. St Louis, The CV Mosby Co, 1972, pp 360-363. 7. Sellers AM, Iliskovitz HD, Lindauer MD: Systemic arterial hypertension, in Conn HL Jr, Horwitz O (eds): *Cardiac and Vascular Diseases*. Philadelphia, Lea & Febiger, 1971, vol II, pp 934-943. 8. Effects of treatment on morbidity in hypertension: Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. Veterans Administration Cooperative Study Group on Antihypertensive Agents. *JAMA* 202:1028-1034, 1967. 9. Effects of treatment on morbidity in hypertension: II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. Veterans Administration Cooperative Study Group on Antihypertensive Agents. *JAMA* 213:1143-1152, 1970.

Only Ser-Ap-Es combines control of fluid volume with hydrochlorothiazide...

Hydrochlorothiazide provides a modest antihypertensive effect through control of extracellular fluid volume, and potentiates the activity of other antihypertensive drugs.[5-7]

(a) Symbolized reduction in circulating fluid volume

plus control of sympathetic activity with reserpine...

Reserpine decreases blood pressure by interfering with the release of norepinephrine at peripheral sympathetic neuroeffector sites.[5-7]

Sympathetic inhibition also produces a central sedative effect especially useful in management of the stress-reactive patient.

(b) Schema of norepinephrine depletion at sympathetic nerve ending

plus direct relaxation of arteriolar smooth muscle with hydralazine...

The unique action of hydralazine lowers blood pressure through direct arteriolar vasodilation to reduce peripheral resistance.[5-7] The decrease in arteriolar resistance is accompanied by maintenance of regional vascular flow, making hydralazine particularly valuable for patients with slightly impaired renal flow.[7]

(c) Diagram of relaxed arteriole

...in a single tablet

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reserpine 0.1 mg
hydralazine hydrochloride 25 mg
hydrochlorothiazide 15 mg

Peripheral neuritis, evidenced by paresthesias, numbness, and tingling, has been observed. Published evidence suggests an antipyridoxine effect and addition of pyridoxine to the regimen if symptoms develop.
Blood dyscrasias, consisting of reduction in hemoglobin and red cell count, leukopenia, agranulocytosis, and purpura, have been reported. If such abnormalities develop, discontinue therapy. Periodic blood counts are advised during prolonged therapy.
Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. Observe patients for clinical signs of fluid or electrolyte imbalance (hyponatremia, hypochloremic alkalosis, and hypokalemia). Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbance such as nausea or vomiting.
Hypokalemia may develop with thiazides as with any other potent diuretic, especially during brisk diuresis, when severe cirrhosis is present, or during concomitant administration of steroids or ACTH.
Interference with adequate oral intake of electrolytes will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity.
Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver diseases or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of salt, except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.
Transient elevations in plasma calcium may occur in patients receiving thiazides, particularly in those with hyperparathyroidism. Pathological changes in the parathyroid gland have been reported in a few patients on prolonged thiazide therapy.
Hyperuricemia may occur or frank gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged. Latent diabetes may become manifest during thiazide administration.
Thiazide drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the post-sympathectomy patient. Thiazides may decrease arterial responsiveness to norepinephrine. This is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.
If nitrogen retention indicates onset of progressive renal impairment, consider withholding or discontinuing diuretic therapy.
Thiazides may decrease serum PBI levels without signs of thyroid disturbance.

ADVERSE REACTIONS
Reserpine: Gastrointestinal—hypersecretion; nausea; vomiting; anorexia; diarrhea. *Cardiovascular*—angina-like symptoms; arrhythmias (particularly when used concurrently with digitalis or quinidine); bradycardia. *Central Nervous System*—drowsiness; depression; nervousness; paradoxical anxiety; nightmares; rare parkinsonian syndrome and other extrapyramidal tract symptoms; CNS sensitization (manifested by dull sensorium, deafness, glaucoma) vertigo, and optic atrophy. *Miscellaneous*—frequently nasal congestion; pruritus; rash; dryness of mouth; dizziness; headache; dyspnea; syncope; epistaxis; purpura and other hematological reactions; impotence or decreased libido; dysuria; muscular aches; conjunctival injection; weight gain; breast engorgement; pseudolactation; gynecomastia; rarely water retention with edema in hypertensive patients.
Hydralazine Common—headache; palpitations; anorexia; nausea; vomiting; diarrhea; tachycardia; angina pectoris. *Less frequent*—nasal congestion; flushing; lacrimation; conjunctivitis; peripheral neuritis, evidenced by paresthesias, numbness, and tingling; edema; dizziness; tremors; muscle cramps, psychotic reactions characterized by depression, disorientation, or anxiety; hypersensitivity (including rash, urticaria, pruritus, fever, chills, arthralgia, eosinophilia, and, rarely, hepatitis); constipation; difficulty in micturition; dyspnea; paralytic ileus; lymphadenopathy; splenomegaly; blood dyscrasias, consisting of reduction in hemoglobin and red cell count, leukopenia, agranulocytosis, and purpura; hypotension; paradoxical pressor response.
Hydrochlorothiazide Gastrointestinal—anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic), pancreatitis. *Central Nervous System*—dizziness, vertigo, paresthesias, headache, xanthopsia. *Dermatologic-Hypersensitivity*—purpura, photosensitivity, rash, urticaria, necrotizing angiitis, Stevens-Johnson syndrome, and other hypersensitivity reactions. *Hematologic*—leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia. *Cardiovascular*—orthostatic hypotension may occur and may be potentiated by alcohol, barbiturates, or narcotics. *Other*—hyperglycemia, glycosuria, hyperuricemia; muscle spasm, weakness, restlessness. When adverse reactions are moderate or severe, reduce dosage or withdraw therapy.

DOSAGE
As determined by individual titration (see box warning).
Usual dosage is 1 or 2 tablets t.i.d. For maintenance, adjust dosage to lowest patient requirement. When necessary, more potent antihypertensives may be added gradually in dosages reduced by at least 50 percent.

HOW SUPPLIED
Tablets (dark salmon pink, dry-coated), each containing 0.1 mg reserpine, 25 mg hydralazine hydrochloride, and 15 mg hydrochlorothiazide: bottles of 100 and 1000.
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CIBA

Report on XYY Screening Held Whitewash

Continued from page 1

mittee on Medical Research a "whitewash."

In a report to the faculty, the committee stated that, in its opinion, Dr. Stanley Walzer, Assistant Professor of Psychiatry at Harvard, has behaved ethically and sensitively in the way in which he has conducted his

See Editorials, Page 11. Also, One Man . . . and Medicine, Page 33.

program of examining the incidence of extra "Y" and "X" chromosomes in newborn boys, and studying the correlation, if any, of the abnormalities with behavior.

Because several of its members were concerned that the possible risks of the study might outweigh its benefits, the Harvard committee also announced that it has asked Dr. Walzer to meet with it to discuss changes that may lessen public criticism.

Dr. Walzer, has been under fire from a group of young Boston Scientists, calling themselves Science for the People, who have charged that boys were found to have XYY chromosome abnormality will be stigmatized for life by the study for possessing what the public has come to know as the "criminal chromosome."

The spokesman for the group, Jonathan Beckwith, Ph.D. a Harvard microbiologist, said that the findings, of the Medical Research Committee, "failed to deal in any way with the substantive objections to the XYY study which we have raised.

'Simply a Whitewash'

"The present recommendations are simply a whitewash of an embarrassing situation; the objections to the study stand unanswered and a source of concern, not only within the Harvard community, but among the general public as well."

Dr. Beckwith and his colleagues—scientists from Harvard and the Massachusetts Institute of Technology—made their charges formally to the medical school last April. They have accused the study of being unscientific on the grounds that parents who are anxious about the effect of the XYY chromosome variation are bound to treat their youngsters in a negative way.

This, they say, is likely to increase the incidence of behavior problems, skewing the results of the study, and harm the child.

The study is unethical, they claim, because of the danger of stigmatizing the boy, because there is no therapy for chromosomal abnormalities, hence no clear-cut benefits to the families participating.

The group has also criticized the research project for manner in which mothers-to-be were asked to consent to the screening. Until recently, the woman was asked to sign the consent form when she was admitted to the hospital, often when she was in labor. The form asked only for permission to test the infant. When an abnormality was found, the parents were informed and asked to participate in the study.

Since the project has been under fire, the form has been rewritten and now fully explains the investigation and its implications. It is given to the mother the day after the delivery and is explained by a member of the research staff.

The Boston Hospital for Women, where the work is being done, mails all the incoming patients a "Bill of Rights," which points out that she is under no obligation to participate in any study, and if asked to do so, she should consult her physician for guidance.

Since the study began in 1968, some 15,000 newborns have been screened for any chromosome abnormality, and children exhibiting variations will be followed into their adolescence in an effort to understand the relationship between the variations and certain types of behavior development.

Similar screening programs are being conducted in Denver and New Haven, in Winnipeg and London, in Canada, and in Denmark and Scotland.

In the Boston investigation thus far, Dr. Walzer and Dr. Park Gerald, Professor of Pediatrics at Harvard, have identified 12 boys with the XYY pattern and 15 with the XXY variation.

Newspaper publicity in the past incorrectly labeled the extra "Y" the "criminality chromosome," because males possessing it were found in penal-mental institutions approximately 20 times more frequently than in the general population.

In the current study, Drs. Walzer and Gerald have found that "only some" boys with either chromosome pattern have begun to exhibit behavioral difficulties; most of them, they hasten to add, "are developing into wonderful kids."

Some XYY boys "seem to be impulsive and to have difficulty in controlling themselves," Dr. Gerald reported at the press conference following the research committee announcement, and, "XYY boys are prone to have speech and language difficulties, although their IQs are normal or even high."

Dr. Walzer told MEDICAL TRIBUNE that he feels chromosome screening is necessary "because you can prevent a lot of hell for these kids by diagnosing early."

"I believe that parents, have a right to know of any chromosome variations and they have a right to watch their child, to make changes in his life, to enrich it anyway they can, and to help him in whatever way is possible," he said.

In Contact With Families

"In a study like this, in which you share genetic information with people, one must be available to them in the future when questions and problems may arise. This particular experimental design allows for that."

Dr. Walzer was referring to the fact that he spends two or three hours every month with each family; at this time, the child is tested and observed. He maintains that he is available for telephone consultation at any time.

This aspect of the study was also criticized by Dr. Beckwith and his group. Because the investigation includes the promise of assistance and counseling in the event that the extra chromosome results in behavior disorders, they contend that worried patients may agree to participate under duress—the offer of professional help.

Dr. Walzer, who is also senior associate in genetics at Children's Hospital Medical Center, does not agree with this assessment of the parents in the study. "It is most arrogant," he said, "to assume that parents are so easily pressured that they cannot make their own decisions, and that investigations that develop such information should not be undertaken because parents cannot handle it."

"Right now, it's almost as if anyone wanting to do an investigation automatically must be thought to be unethical, and from that point on he must prove himself ethical," Dr. Walzer added.

"I know the consultation and the advice I have sought at this phase of the work, and the presentation I have made. I know that I am not unethical. I have a great sensitivity to that—that's the charge that has hurt the most."

Illustrator In Air Force

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Q. & A. Roundup of Data on XYY Karyotype

Medical Tribune Staff

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How does this incidence compare with that of other sex chromosome anomalies?

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In 1965, chromosome studies were made at a Scottish maximum security hospital of 315 of the 342 men housed in wings allocated to the mentally subnormal and mentally diseased. Nine of these men had the XYY pattern, thus indicating an incidence in this prison population of nearly 3 per cent.

Do later studies back up this finding?

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Findings in individual studies have ranged from no XYYs among 31 mentally ill men with criminal records in Greece to 10 such men among 255 mentally subnormal men in an English security institution. Chromosome screening of about 1,100 boys in Scottish schools for problem children and another 607 older boys in institutions for delinquents identified five XYYs, for an over-all incidence of about three per 1,000.

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Dr. Lejeune testified that "the bearer of an extra chromosome is a sick man," and noted the frequency of the XYY pattern among prisoners. But he then emphasized: "There is no such thing as a born criminal. It is not a chromosome which causes the commission of a crime but an ensemble of reactions along with an absence of control."

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Aren't institutional findings apt to be biased in some respects?

Yes. Admission procedures differ from place to place, and everyone is aware that only a small proportion of the people who commit antisocial acts wind up behind bars.

Additionally, it is thought that the tallness of the average XYY may be a factor in sentencing. Because of his size, he may be considered—perhaps unconsciously—more of a "threat" than the XY who has shown deviant behavior.

What is known about XYY males who are not in institutions?

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Report on XYY Screening Held Whitewash

Continued from page 1

mittee on Medical Research a "whitewash."

In a report to the faculty, the committee stated that, in its opinion, Dr. Stanley Walzer, Assistant Professor of Psychiatry at Harvard, has behaved ethically and sensitively in the way in which he has conducted his

See Editorials, Page 11.
Also, One Man . . . and Medicine, Page 33.

program of examining the incidence of extra "Y" and "X" chromosomes in newborn boys, and studying the correlation, if any, of the abnormalities with behavior.

Because several of its members were concerned that the possible risks of the study might outweigh its benefits, the Harvard committee also announced that it has asked Dr. Walzer to meet with it to discuss changes that may lessen public criticism.

Dr. Walzer, has been under fire from a group of young Boston Scientists, calling themselves Science for the People, who have charged that boys were found to have XYY chromosome abnormality will be stigmatized for life by the study for possessing what the public has come to know as the "criminal chromosome."

The spokesman for the group, Jonathan Beckwith, Ph.D. a Harvard microbiologist, said that the findings, of the Medical Research Committee, "failed to deal in any way with the substantive objections to the XYY study which we have raised.

'Simply a Whitewash'

"The present recommendations are simply a whitewash of an embarrassing situation; the objections to the study stand unanswered and a source of concern, not only within the Harvard community, but among the general public as well."

Dr. Beckwith and his colleagues—scientists from Harvard and the Massachusetts Institute of Technology—made their charges formally to the medical school last April. They have accused the study of being unscientific on the grounds that parents who are anxious about the effect of the XYY chromosome variation are bound to treat their youngsters in a negative way.

This, they say, is likely to increase the incidence of behavior problems, skewing the results of the study, and harm the child.

The study is unethical, they claim, because of the danger of stigmatizing the boy, because there is no therapy for chromosomal abnormalities, hence no clear-cut benefits to the families participating.

The group has also criticized the research project for manner in which mothers-to-be were asked to consent to the screening. Until recently, the woman was asked to sign the consent form when she was admitted to the hospital, often when she was in labor. The form asked only for permission to test the infant. When an abnormality was found, the parents were informed and asked to participate in the study.

Since the project has been under fire, the form has been rewritten and now fully explains the investigation and its implications. It is given to the mother the day after the delivery and is explained by a member of the research staff.

The Boston Hospital for Women, where the work is being done, mails all the incoming patients a "Bill of Rights," which points out that she is under no obligation to participate in any study, and if asked to do so, she should consult her physician for guidance.

Since the study began in 1968, some 15,000 newborns have been screened for any chromosome abnormality, and children exhibiting variations will be followed into their adolescence in an effort to understand the relationship between the variations and certain types of behavior development.

Similar screening programs are being conducted in Denver and New Haven, in Winnipeg and London, in Canada, and in Denmark and Scotland.

In the Boston investigation thus far, Dr. Walzer and Dr. Park Gerald, Professor of Pediatrics at Harvard, have identified 12 boys with the XYY pattern and 15 with the XXY variation.

Newspaper publicity in the past incorrectly labeled the extra "Y" the "criminality chromosome," because males possessing it were found in penal-mental institutions approximately 20 times more frequently than in the general population.

In the current study, Drs. Walzer and Gerald have found that "only some" boys with either chromosome pattern have begun to exhibit behavioral difficulties; most of them, they hasten to add, "are developing into wonderful kids."

Some XYY boys "seem to be impulsive and to have difficulty in controlling themselves," Dr. Gerald reported at the press conference following the research committee announcement, and, "XYY boys are prone to have speech and language difficulties, although their IQs are normal or even high."

Dr. Walzer told MEDICAL TRIBUNE that he feels chromosome screening is necessary "because you can prevent a lot of hell for these kids by diagnosing early."

"I believe that parents, have a right to know of any chromosome variations and they have a right to watch their child, to make changes in his life, to enrich it anyway they can, and to help him in whatever way is possible," he said.

In Contact With Families

"In a study like this, in which you share genetic information with people, one must be available to them in the future when questions and problems may arise. This particular experimental design allows for that."

Dr. Walzer was referring to the fact that he spends two or three hours every month with each family; at this time, the child is tested and observed. He maintains that he is available for telephone consultation at any time.

This aspect of the study was also criticized by Dr. Beckwith and his group. Because the investigation includes the promise of assistance and counseling in the event that the extra chromosome results in behavior disorders, they contend that worried patients may agree to participate under duress—the offer of professional help.

Dr. Walzer, who is also senior associate in genetics at Children's Hospital Medical Center, does not agree with this assessment of the parents in the study. "It is most arrogant," he said, "to assume that parents are so easily pressured that they cannot make their own decisions, and that investigations that develop such information should not be undertaken because parents cannot handle it."

"Right now, it's almost as if anyone wanting to do an investigation automatically must be thought to be unethical, and from that point on he must prove himself ethical," Dr. Walzer added.

"I know the consultation and the advice I have sought at this phase of the work, and the presentation I have made. I know that I am not unethical. I have a great sensitivity to that—that's the charge that has hurt the most."

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Is the boy with an XYY makeup at risk of showing deviant behavior?

The experts' answers range from a flat "No" or "Yes" to "Nobody knows" or "It all depends." Most investigators do agree than XYY males are found in mental-penal institutions at a frequency much greater than the "background" incidence of one per 1,000 newborn males.

But as many investigators point out, a child's behavior is influenced by numerous factors, including complications that occurred during fetal life or at birth, social class, family stability, parental supervision, genetic makeup.

Instead of insisting on nature or nurture, they think the effects of both must be taken into account.

F. G.

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And should you choose to prescribe Valium, you should also keep this information in mind. Valium is generally well tolerated in the recommended dosage ranges. However, the physician should be aware of the possibility of side effects in some patients and should consult complete product information before prescribing.

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Medical Tribune

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In Science, Derogation Is Not Debate

AS AN ARTICLE, "The XYY syndrome: a dangerous myth" (Jon Beckwith, Ph.D., and Jonathan King, Ph.D., *New Scientist* 64:474-Nov. 14, 1974) starts by projecting a significant scientific issue in a suitable forum. When it reviews genetic reports on challenges, methodologies and interpretation of studies in this area, it is a valid exercise of the scientific method. When it proceeds into a derogatory discourse and attack upon fellow scientists, it is not. Scientific derogation is not scientific debate.

After criticizing the projection of opinions as facts, Beckwith and King then present their own assumptions—as facts. In so doing, they weaken the thrust of their argument, to wit, that social unrest and anti-social behavior are not solely the results of deviant or genetic abnormality but also significantly relate to poor social and economic conditions, poor standards of living and of education, of poor health. One can agree that it is dangerous "to reinforce a growing tendency to explain away the problems of society in terms of the genes or biology of individuals" without also accepting as a correlate that investigators who seek to study the relationship of genetic and physiologic factors to behavior should be prevented from doing such research.

One can find the methodology of a study unacceptable without challenging the integrity or good faith of a fellow scientist with a differing opinion. It is as unacceptable as it is unbecoming to science to use one of its forums to charge "subtle coercion" on the part of others even as one uses the not-so-subtle coercion of the law courts and sensational press publicity to halt the research of those with different beliefs. It is unfair to intimate without the strongest evidence that the other investigators' procedures constitute a dangerous "self-fulfilling prophecy". One need not accept a bland assertion charging the honest efforts by physicians seeking to inform patients or family to the best of their ability to be a dangerous procedure. "There is ample evidence that this sort of attitude toward the child may endanger the very behavior they fear or create other unpredictable problems." Is the evidence really definitive?

One cannot justify condemnation by geneticists that "psychiatrists' intervention may be creating more problems for the children than would have occurred if they had been left alone." Is this not the arrogation of psychiatric expertise by geneticists? Are they expressing guilt feelings in regard to the Pandora's Box which they may believe they, as geneticists, have opened? The authors' choice of those studies which they deem "to be worthwhile" is a matter of opinion; a charge as to studies which they believe pose "serious risk . . . or would be positively harmful to the subjects involved" is likewise based on an assumption that is projected in a manner damaging to science, their fellow scientists, to patients, and to themselves.

Despite any areas of agreement with some elements of their article, we can find no justification for the authors' going beyond the realm of scientific debate to derogatory ad hominem attacks, and even less for carrying such attacks from the forums of science into the judicial arena in an attempt to stop the research of other investigators. To do so is to do exactly what the authors charge to others: "wasting society's resources on poorly conceived and ideologically" biased battles.

Such actions will delay the clarification of the influences of genetics as well as environmental factors on behavior. They will distract from and not add to a concentration on those aspects of our "social and economic structure" which generate medical as well as social and behavioral problems. A.M.S.

Whose Ox Is Gored By Surgery?

AN IRONIC conjunction of news stories announced a new heart transplant operation by Dr. Christiaan Barnard, i.e., implant of a second left heart, almost simultaneously with the *death of Louis B. Russell*, world's longest surviving heart recipient, who had undergone heart transplant surgery more than six years ago. The headlines of the new transplant story, "Barnard Is Eager To Try 2nd Heart Surgery Again" and "Barnard Is Eager for 2nd Operation," just do not convey the sense that it is the patient, not the surgeon, who is primarily at risk.

A case in point, and such cases are many, was the recent experience of a patient, himself an internist, who recounted his own shattering interview with his cardiac surgeon, a man of great eminence. Because of increasing angina he consulted the surgeon, who had performed an earlier operation on him, the Vineberg procedure, to discuss the feasibility of a coronary bypass. The undertaking is formidable for the Vineberg procedure, matting epicardium to extracardiac tissues, raises problems of bleeding and freeing up the coronary arteries for bypass. The surgeon said he would be willing to take the risk. The patient understandably reacted quite differently. "Our risk, he said, is a statistic, my risk is that I live or die.

P.S. The operation was not done and the patient lives. In these days of informed consent it is all very well, indeed necessary, to tell the patient of the potential risks of surgical or medical intervention. When one takes another's life in one's hands, psyche and soma both demand solicitude. The cutting edge of what one says to a patient is no less sharp than the scalpel, and requires quite as much exercise in discretion and delicacy as what one does. R.G.

"Sorry I'm late, but it took them about a week to determine I was legally dead."

LETTERS TO TRIBUNE

Medical Insanity?

In your "Editorial Capsules" (MT, Nov. 27) Harold C. Hodge, Ph.D. was quoted as follows: ". . . Fluoride is accepted as a safe and effective prophylactic agent in the prevention of dental caries whose benefits, strikingly apparent in childhood, continue into adult life with continued use." This statement encompasses the same political propaganda expounded over the years to make fluoridation more palatable to physicians and dentists.

The true facts of the fluoridation hoax are revealed in the book "Fluoridation and Truth Decay" which I have co-authored with Gladys Caldwell of La Crescenta, Calif. The book exposes fluoridation as medical insanity and the greatest consumer fraud of this century.

PHILIP E. ZANFAGNA, M.D.
Lawrence, Mass.

Ambulatory Surgical Care

I should like to comment on your article concerning ambulatory surgical facilities (MT, Nov. 13).

It should be emphasized that the movement for free standing ambulatory surgical care is growing throughout the United States. Those of us who are involved in it are terribly concerned over the same issues which bother Dr. Hinds and Dr. Welch. We, too, are concerned over the over utilization of such facilities and the quality controls that must be built into them to make them acceptable to the American public. The first meeting of the Society for the Advancement of Free Standing Ambulatory Surgical Care took place in Phoenix in early November and at that time we dedicated ourselves to the construction of standards of care which would be appropriate for facilities that are not associated with hospitals.

We must let the American people know that there is no stigma attached to receiving surgical care in a free standing ambulatory surgical facility; that the care rendered in such a facility under the proper guidelines is infinitely better than what one can get in hospital settings. The personal care, warmth, convenience, high standards and reduced cost have been found to be eminently acceptable to the patient population in the city of Wichita. We are amply demonstarting that the Phoenix Surgicenter was no accident, not an aberration which was only going to succeed in Phoenix. We have found their model to be reproducible and the public of our city to be just as responsive.

Any changes in the health care system, regardless of who they affect, are going to be met with resistance by the traditionalists. This is understandable. Blind opposition, however, is not constructive and the public does deserve an alternative. Free standing ambulatory surgical facilities, in those communities which are fortunate enough to have them, give their local population their free choice of such an alternative. This is entirely consistent with the American way of life.

Mr. James Latham states that when free standing centers compete with hospital units the cost of the system is upped in toto. We do not believe this to be true. So far no factual data to support his point of view or our point of view has been forthcoming. Such a study is now underway by the Department of HEW. We hope that within the next four or five years we will have a specific answer to this knotty problem.

M. ROBERT KNAPP, M. D.
Wichita, Kans.

Surgicenter®

Your article (MT, Nov. 13) uses the term "Surgicenter" in referring to all outpatient ambulatory surgical facilities. "Surgicenter" is a registered name. We would greatly appreciate it if you would acknowledge this.

WALLACE A. REED, M.D.
Surgicenter
Phoenix, Ariz.

Bloopus Erythematosus—

With all due respect to Dr. Freddy Homburger, (MT, Dec. 11), I too studied Latin. Not his seven and one-half years, but a mere four years.

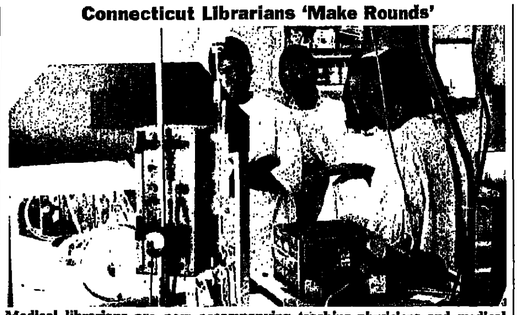
In college, I also studied, of all things, one year of GREEK.

I think if Dr. Homburger would consult any medical dictionary—nay, even Webster—he would find the root "erythro" is Greek, meaning "red", and the root "osis" is also Greek, meaning, in this context, "abnormal or diseased condition."

All of which proves the old adage, "The Greeks had a word for it."

ALAN E. VAN SCIVER, M. D.
Larchmont, New York

Connecticut Librarians 'Make Rounds'



Medical librarians are now accompanying teaching physicians and medical students on rounds at the University of Connecticut Health Center. By actually "making rounds," the librarians can efficiently answer requests from doctors and students for articles and locate other helpful material.

Massive Glucose Infusions Shown Lifesaving in Shock

Continued from page 1

for 30 hours. In the first group of studies all treated animals received continuous I.V. infusions of 50 per cent dextrose, starting 15 minutes after endotoxin injection and continuing for five hours, "with infusion rates adjusted to maintain blood glucose levels at control preshock values."

Eight of 11 control animals given endotoxin alone died within 30 hours, Dr. Hinshaw reported. He noted that the three that did not die all became "only mildly hypoglycemic." The nine treated controls all survived. "Heart rate, rectal temperature, and pH were notably elevated within five hours in animals receiving glucose."

In the second group of studies, glucose infusions were started only after hypoglycemic levels reached 40 mg. per cent. Treatment to restore glucose levels and maintain them at control values was continued for seven hours after endotoxin shock and "prevented death in all five animals." Ten controls died.

Dr. Hinshaw added that massive bloody diarrhea observed in the control animals was not seen in the glucose-treated dogs. In addition, the treated animals were "generally more alert and demonstrated an increased level of well-being during the postshock recovery period."

Dr. Hinshaw commented: "We were surprised by the huge amounts of glucose we had to give in order to keep up with the animals' requirements. Far more was needed than anyone would have predicted. It was as if the 'internal fires of metabolism' were burning with forest fire intensity. We found that only concentrated glucose could be used; otherwise, the animals would die of pulmonary edema."

In an interview, the investigator said that total glucose turnover in endotoxin shock animals occurred every five minutes. "The turnover is so great it's like diabetes."

Ignored by Most Clinicians

"Most clinicians don't measure glucose in shock because they don't think it plays a major role. Hyperglycemia in man is readily observed and interpreted accordingly. But the fact is that nobody has been doing insulin studies in shock. We have followed the dog experiments with primate studies, and we're observing hypoinsulinemia in baboons and rhesus monkeys in shock."

He added that other shock investigators may have missed the hypoglycemia because their glucose studies terminated at six hours, and "we're seeing hypoglycemia from the sixth to the 24th hour."

He told MEDICAL TRIBUNE that his team was "enormously encouraged" by a recent report from a University of Munich group describing "hypoglycemia in human shock for the first time." The studies were conducted by Dr. R. Rackwitz of the university's medical clinic.

Dr. Hinsaw stressed that shock is a multifactorial problem, and that massive glucose infusions are not "the total answer," but "we feel that we've got onto one of the mainline problems. With this gap plugged, we can repeat almost all of the other therapies. It opens up for the first time a possible avenue of approach to the problem of shock."

Coauthors were Drs. Ruth T. Brantley, Marvin D. Peyton and L. J. Greenfield; J. J. Coalson, Ph.D., and L. T. Archer and M. R. Black.

NIH Revises Booklet

Medical Tribune Report

BETHESDA, MD.—NIH's Clinical Center has issued a revised edition of its booklet for physicians, *Current Clinical Studies and Patient Referral Procedures.*

Mitral Valve Calcification in Aortic Stenosis

Medical Tribune World Service

BUENOS AIRES—Congestive heart failure and abnormal conduction and rhythm disturbances often indicate the secondary presence of mitral valve calcification in cases of idiopathic hypertrophic subaortic stenosis, Dr. Emilio R. Giuliani, Associate Professor of Cardiology at the Mayo Clinic, told the seventh World Congress of Cardiology.

While the association of the two diseases is not common—Dr. Giuliani found an incidence of seven per cent among 150 Rochester, Minn., patients with proven idiopathic hypertrophic subaortic stenosis—the presence of both often leads the physician astray to a diagnosis of primary mitral valve disease.

Co-authors of the study were Drs. Abdul J. Tajik, William H. Wiedman, Robert O. Brandenburg, and Dwight C. McGoon.

According to Dr. Giuliani, out of 11 patients with calcification confirmed by fluoroscopic examination, over half presented in advanced congestive heart failure, eight showed various degrees of mitral regurgitation, detected by cardiac catheterization, and six out of the eleven proved to be in atrial fibrillation according to their EKGs.

Of the seven patients placed on the beta-adrenergic blocking agent propranolol—the initial treatment of choice —six have been doing well for periods of six months to four years while one patient died suddenly.

When chemotherapy fails, surgery is indicated, Dr. Giuliani said. Of the three patients who underwent surgery (an additional patient died awaiting surgery), one patient is doing well, another died following replacement of his mitral valve and the third required a pacemaker because of complete heart-block. "It is likely," Dr. Giuliani predicted, "that artificial pacing may find a greater role in this small group of patients."

Septal Myectomy

► In a second study, the same team of investigators reported that experience with transaortic septal myectomy in cases of idiopathic hypertrophic subaortic stenosis demonstrated that the surgery can be accomplished at relatively low risk and can produce significant, long-term symptomatic relief.

In a group of 43 patients operated on from 1958 through 1972, the overall mortality rate for the period of follow-up—ranging from 18 to 142 months—was 25 per cent, including three patients who died early after additional operative procedures and four late deaths, occurring suddenly at 1½, 2, 4 and 10 years postoperatively.

Of the 43 patients, the majority (21) had resection of a wide wedge of intraventricular muscle via transaortic approach while 19 had myectomy, accomplished through a ventriculotomy incision, alone or in combination with a transaortic incision, and three patients had additional procedures.

Of the 28 patients who were followed up for recurring symptoms, 12 are asymptomatic, and in the rest, syncope has been eliminated.

4-Drug Regimen With Adriamycin Aids Sarcomas

Continued from page 1

among patients showing a response to adriamycin. More than one-fourth of the adriamycin responders achieved five-year survival after being given this drug alone, and close to half did so when given adriamycin plus DIC.

Dr. Gottlieb said that "it is too early" to estimate survival times for patients on the four-drug regimen but noted that a year from the close of the study only one complete responder and eight partial responders have succumbed, "suggesting that over-all survival will be excellent."

The Southwest Oncology Group is now comparing this regimen with one in which actinomycin D is substituted for DIC. Such a comparison had not previously been feasible, Dr. Gottlieb noted, because many patients in earlier studies had already been treated with actinomycin D. The successes of adriamycin combinations mean that "we are now seeing patients without prior chemotherapy," he pointed out.

Preliminary Data Favor DIC

Although he emphasized that more time will be needed for a complete evaluation of results, he cited preliminary data to indicate that patients given the combination with DIC "appear to be doing a little better."

Of the evaluable patients, those receiving DIC in combination with adriamycin, cyclophosphamide, and vincristine have achieved a 15 per cent complete remission rate and a 62 per cent over-all response rate. Those for whom the fourth drug has been actinomycin D have achieved a 5 per cent complete and a 51 per cent over-all response rates.

The gains seen from all the regimens containing adriamycin have led M.D.A.H. investigators to try such combination chemotherapy "at the time of initial diagnosis, as an adjuvant to surgery and radiotherapy in patients at high risk for recurrence," Dr. Gottlieb said.

Approximately 30 patients with soft-tissue sarcoma have been treated by this protocol over the past year, he added, and only one relapse has occurred.

Apresoline® (hydralazine)...where the action is in treating hypertension

Apresoline lowers blood pressure by exerting a peripheral vasodilating effect through a direct relaxation of arteriolar smooth muscle.

An antihypertensive idea whose time has come

Doctors who treat hypertension are increasingly interested in the one oral drug that has a mechanism of action exclusively its own—Apresoline.

Apresoline is in an antihypertensive class by itself because it reduces blood pressure through a unique mechanism. Acting at the ultimate site of hypertension, it directly relaxes arteriolar smooth muscle to decrease peripheral vascular resistance and arterial pressure. As blood pressure falls, there is an accompanying rise in cardiac output and rate.

Apresoline also maintains or increases renal and cerebral blood flow.

Apresoline minimizes postural hypotension

Nickerson[1] describes the action of Apresoline as follows:

"A preferential effect on arterioles, as compared to veins, allows the increase in cardiac output and minimizes postural hypotension; the latter is much less than that produced by agents blocking sympathetic nerves."

Apresoline avoids side effects associated with other agents

Such untoward reactions as drowsiness, lethargy, sedation, sexual dysfunction, and exacerbation of mental depression are not usually encountered with Apresoline. However, as with any antihypertensive agent, hydralazine should be used with caution where advanced renal damage exists.

Apresoline helps tailor the regimen to the patient

When Apresoline is added to an existing antihypertensive regimen, it introduces a different and complementary pharmacologic approach to the control of your patient's hypertension.

Apresoline thus affords the physician a variety of combinations with which he can construct regimens more closely molded to individual requirements. According to Freis,[2] such a combination of drugs, each with a different antihypertensive mechanism, is the most effective way to control blood pressure. This may also permit lower drug dosages.

Apresoline lends itself admirably to the contemporary antihypertensive rationale and its therapeutic goals: more vigorous and more effective control of blood pressure through a plurality of mechanisms.

Apresoline: used effectively in the VA studies

Apresoline was one of the three basic drugs used in two published VA cooperative studies.[3,4]

References: 1. Nickerson M: Antihypertensive agents and the drug therapy of hypertension, in Goodman LS, Gilman A (eds): *The Pharmacological Basis of Therapeutics*, ed 4. New York, The Macmillan Company, 1970, p 729. **2.** Freis ED: *Hypertension: a controllable disease. Clin Pharmacol Ther* 13:627-632, 1972. **3.** Effects of treatment on morbidity in hypertension: Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg, Veterans Administration Cooperative Study Group on Antihypertensive Agents. *JAMA* 202:1028-1034, 1967. **4.** Effects of treatment on morbidity in hypertension: II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg, Veterans Administration Cooperative Study Group on Antihypertensive Agents. *JAMA* 213:1143-1152, 1970.

Next page: Apresoline (hydralazine) and the Hypertension Task Force

Apresoline® hydrochloride
(hydralazine hydrochloride)

TABLETS

INDICATIONS
Essential hypertension, alone or as an adjunct.
CONTRAINDICATIONS
Hypersensitivity; coronary artery disease; mitral valvular rheumatic heart disease.
WARNINGS
Chronic administration of doses over 400 mg per day may produce an arthritis-like syndrome leading to a clinical picture simulating acute systemic lupus erythematosus. This may also occur at lower doses. Most of these reactions are reversible upon withdrawal of therapy; but long-term treatment with steroids may be necessary and residua have been detected many years later. Complete blood counts, L.E. cell preparations and antinuclear antibody titer determinations are indicated before and periodically during prolonged therapy, even though patient is asymptomatic. These studies are also indicated in the presence of any unexplained symptoms.
Use MAO inhibitors with caution.

Usage in Pregnancy
The drug should be used only when, in the judgment of the physician, it is deemed essential to the welfare of the patient.
PRECAUTIONS
Use cautiously in suspected coronary artery or other cardiovascular diseases, cerebral vascular accidents, and advanced renal damage. Postural hypotension may occur and the pressor response to sympathomimetic amines may be reduced.
Peripheral neuritis, evidenced by paresthesias, numbness, and tingling, has been observed. Published evidence suggests an antipyridoxine effect and addition of pyridoxine to the regimen if symptoms develop.
Blood dyscrasias, consisting of reduction in hemoglobin and red cell count, leukopenia, agranulocytosis, and purpura, have been reported rarely. If such abnormalities develop, discontinue therapy. Periodic blood counts are advised during prolonged therapy.
ADVERSE REACTIONS
Common: Headache; palpitations; anorexia; nausea; vomiting; diarrhea; tachycardia; angina pectoris. *Less frequent:* Nasal congestion; flushing; lacrimation; conjunctivitis; peripheral neuritis, evidenced by paresthesias, numbness, and tingling; edema; dizziness; tremors; muscle cramps; psychotic reactions characterized by depression, disorientation, or anxiety; hypersensitivity (including rash, urticaria, pruritus, fever, chills, arthralgia, eosinophilia, and, rarely, hepatitis); constipation; difficulty in micturition; dyspnea; paralytic ileus; lymphadenopathy; splenomegaly; blood dyscrasias, consisting of reduction in hemoglobin and red cell count, leukopenia, agranulocytosis, and purpura; hypotension; paradoxical pressor response.

DOSAGE
Initiate therapy in gradually increasing dosages; adjust according to individual response. Start with 10 mg 4 times daily for the first 2 to 4 days, increase to 25 mg 4 times daily for balance of first week. For second and subsequent weeks, increase dosage to 50 mg 4 times daily. For maintenance, adjust dosage to lowest effective level.
The incidence of toxic reactions, particularly the L.E. cell syndrome, is high in the group of patients receiving large doses of Apresoline.
In a few resistant patients, up to 200 mg Apresoline daily may be required for a significant antihypertensive effect. In such cases, a lower dosage of Apresoline combined with a thiazide, reserpine, or both may be considered. However, when combining therapy, individual titration is essential to insure the lowest possible therapeutic dose of each drug.
HOW SUPPLIED
Tablets, 10 mg (pale yellow, dry-coated); bottles of 100 and 1000.
Tablets, 25 mg (deep blue, dry-coated); bottles of 100, 500 and 1000.
Tablets, 50 mg (lilac, dry-coated); bottles of 100, 500 and 1000.
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Consult complete literature before prescribing.

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One Man... and Medicine

ARTHUR M. SACKLER, M.D.,
International Publisher, Medical Tribune

"The Case of the XYY Chromosomes" RESEARCH AND PATIENTS RIGHTS - PART I

First, we had "full disclosure." Good!
Then, we had "informed consent." Good!
And now, we have "The Case of the XYY Chromosomes."

There seems to be a madness loose—a pseudo-science, fundamentally an anti-science, which justifies its anti-intellectual means by its proclaimed social goals. The attacks of these anti-scientists seem to follow a simple format. Pick an emotionally labile situation, make emotionally laden charges in the name of The People, claim that The People need your protection . . . link up with like-minded attorneys . . . launch "consumer advocacy" litigation and do all this with sensational headline-provoking charges at a press conference. Mix these with an attack on the ethics of a sacrificial scapegoat. It makes no difference if he is a colleague or a fellow scientist, if his work is valid or cleared through all the requisite committees.

Assault on Medical Science

Today, Boston—historic cradle of American liberties—becomes the scene of a latter-day version of an earlier-day witch hunt. Boston doctors—pediatricians and psychiatric researchers, OBS/GYN men and residents—are exposed to civil litigation and worse. Sadly, Boston is not alone; in New York and Michigan, men devoted to biomedical research, men of achievement and sensitivity such as Krugman and Jacques Gottlieb, come "under fire."

At Harvard Medical School a child psychiatrist undertook a study of children with sex chromosomal anomalies. He wanted to determine what if any untoward behavioral effects were related to an extra X or Y chromosome and whether, if such existed, early recognition and appropriate therapy would be helpful. In the past, this investigator had saved a number of unborn children with XXY chromosome pattern diagnosed by amniocentesis. He has found that the reading difficulty and academic failure reportedly associated with XXY chromosome makeup might be overcome by early recognition and appropriate therapy. Now he is exposed to vicious public attacks for his XYY research.

Circumventing Scientific Review

These attacks have circumvented what should have been a calm and considered scientific dialogue within the traditional forums of scientific exchange and peer review. Our present day Torquemadas apparently find nothing wrong in creating situations wherein research physicians and their families are exposed to anonymous abusive and threatening phone calls: "You fascist pig . . . you should be destroyed." One would think that science has enough to contend with, such as the insensitive genetic "charges" of Shockley and Jensen. One would also expect a greater sensitivity in the area of genetic medicine as one recalls our experience with sickle cell anemia—the blasts of national publicity and screening projects, the unfulfilled hopes and the ultimate unhappy residue of fear and dissatisfaction.

If one looks closely at the XYY case in Boston, one comes to some rather disturbing conclusions. The present protestors challenge the ethics of research in the early stages of life. Protestors from the other end of the political spectrum have just recently constricted, if not brought to a halt, studies involving both human fetus and fetal tissue. We have previously acknowledged the rights of the "Right-To-Life" groups to hold to their beliefs and to their own dogmas even as we have questioned their right to impose either or both upon those who have other beliefs and convictions. In the last few years research in mentally defective children has been attacked. The question of "informed consent" for any child has been raised. Clearly, as to "informed consent" for children, we enter a legal thicket of problems—who can give consent for the nonviable fetus, the unborn child, the newly born child or, for that matter, any child? It can be argued that the rights of an individual child cannot be placed in jeopardy, even by the child's parents.

Potential for Harm

The danger of this position is quite clear; under such circumstances one can deny to any minor not only *participation in research but the potential* benefits of such research because there is a potential for harm in virtually all therapeutic procedures. Such a *reductio ad absurdum* can undermine many preventive and prophylactic health measures, resting as they do on immunologic procedures. Even now, fear of such challenges have restricted research and therefore the determination of proper infants' and children's doses in a wide range of new drugs.

As we have said before, the ultimate end of such an attitude is to guarantee to my children a very questionable right—the right to suffer and die. I object to the preservation of such a dubious right.

Next Week

Dr. Sackler discusses research and patient's rights, full disclosure, and what true "science for people" calls for.

New Breast Prosthesis

A silicone-gel breast prosthesis that simulates normal breast tissue in weight, balance, texture, and movement has been developed at the University of Michigan. Unlike most other breast prostheses, it requires no corseting other than a regular bra and can be worn in the water.

Miami Students Are Offered Oral Exam in Surgery

Medical Tribune Report

CHICAGO—Substitution of an oral examination for a written essay will form part of the final grade for surgical students who elect it at the University of Miami School of Medicine.

The decision was made following an experiment in which 160 juniors voted overwhelmingly to adopt it.

In the experiment, faculty, house staff, seniors, and juniors were asked to submit clinical questions based on 70 lectures by the faculty. A total of 150 questions were generated and senior students made the selection of the final 70.

"Criteria for good questions were that they were asked how to diagnose or what to do in given situations," said Dr. Bernard S. Linn, Associate Professor of Surgery, who presented the report to the Association of American Medical Colleges.

The student was examined by two teams, each consisting of one faculty, one resident, and one senior. Six teams were assembled in six rooms on two afternoons during the last week of clerkship. A student was seen for 15 minutes by one team, and after a 15 minute break, by the other.

"Every effort is made to put the student at ease, such as having coffee and making the process conversational," said Dr. Linn. "The student picks a card from the 35 that are placed face down on a table. He may peremptorily discard up to two questions. About three questions are covered in 15 minutes. He is rated on level of knowledge and on the ability to use the knowledge *clinically*."

Dr. Linn said the system places the student at the center of the learning process. If the students acquire the skills of self-directed learning, he pointed out, it is more likely they will continue to use them long beyond graduation from medical school.

Tribune Economic Analysis

Antitrust Action Should Not Hurt AT&T Holders

By Elliot Janeway
Consulting Economist

Neither stockholders nor bondholders of AT&T are in any danger of being victimized by the government's antitrust action.

The market levels of American Telephone and Telegraph's securities—its bonds, convertibles, and stocks—fluctuate in response to money conditions. When interest rates are high, all the securities of the telephone company suffer. When interest rates are low, all of them benefit.

Intolerable interest rates and onerous government regulation go together—it's a double or nothing proposition. Once the pendulum swings interest rates down again, it will turn government regulation constructive once more. The next bull market will start in response to this double push. It will accelerate by the time the government's antitrust complaint is ready for adjudication.

All the "money market" stocks follow the bond market. Telephone bonds lead it. Once the bond market becomes hospitable again for money looking for work, the stock market will celebrate its reunion with money coming back to play.

Telephone bonds and stock will continue paying their way by current money market standards and will start doing much better the moment money conditions become tolerable.

However, the government's action is guaranteed to help keep the investing public away in droves. There's no way for the stock market to regain its lost stride until the public returns.

Can we expect a cut in Federal taxes in 1975? Or has inflation replaced the Vietnam War?

Dr. M.B., Milwaukee, Wis.

There's no chance of a tax cut in 1975, although there is some chance of selective tax incentives. It's more realistic to say that the inflation started by the Vietnam war lives on after it.

Are electronic stocks a good buy today?

Dr. Ham Operator, New York

No stocks selling only yesterday at high multipliers of earnings and low returns on dividends are a good buy.

German firms, their dollars increased 30% by dollar devaluation, are investing heavily in the United States, and more heavily in South America and Asia. Are we not going to suffer from this?

Dr. Fred W., New Orleans

Not at all. Money invested in America will bring dollars back and tie them down, strengthening the dollar and helping to offset inflation. Money invested in South America and Asia will be lost, weakening Germany, our number one competitor in Europe.

Resignations Renew Call for Fed. Health Dept.

Continued from page 1

fare," declared Rep. Paul G. Rogers (D.-Fla.), Chairman of the House Subcommittee on Public Health and Environment. "Health has to be taken out of the political system."

He added that the country's health programs "are being conducted out of the Office of Management and Budget, not by the health professionals."

Dr. Russell B. Roth, former president of the American Medical Association, noting that the A.M.A. favors a "free-standing Department of Health, with cabinet status," said the resignations underscore the association's stand. "Dr. Edwards has been unable to fight for his priorities as he sees them, because he is subsidiary to the top officials in H.E.W."

Stone Not on 'Team'

Ironically, Dr. Edwards' resignation came only a few days after he had asked Dr. Stone to resign, a move that stemmed from differences over the respective roles of the NIH and HEW. In an interview, Dr. Edwards told MEDICAL TRIBUNE that Dr. Stone had not served as a "member of the team." "We feel strongly that, once policies are adopted [within HEW], the director of NIH should be an advocate of those policies. Dr. Stone has gone to the scientific community to attack decisions that were taken."

He said the "breakdown of communications" between himself and Dr. Stone led to "mutual agreement" that Dr. Stone should withdraw.

Four days later Dr. Edwards announced his own resignation, after twenty months in office. Prior to his last appointment, he was Commissioner of the Food and Drug Administration for nearly four years. He has accepted a post as senior vice president of Becton, Dickinson & Co., of Rutherford, N.J., a medical supply manufacturer.

Dr. Stone, former dean of the University of New Mexico School of Medicine, was appointed 18 months ago, after the abrupt firing of Dr. Robert Q. Marston as NIH chief. Dr. Marston had opposed efforts by the Nixon administration to reduce funding for medical research and training of research scientists.

Three Nobel laureates at NIH and three NIH chiefs issued a joint statement assailing Dr. Stone's firing as "one more indication of the degree to which NIH can be vulnerable to unwarranted and counterproductive political control."

The statement was made public at a press conference here by Drs. Christian Anfinsen, Julius Axelrod and Marshall Nirenberg, Nobel Prize winners, and Franklin Neva, Chief, Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Disease; Robert Goldberger, Chief, Laboratory of Biochemistry, National Cancer Institute; and Earl Stadtman, Chief, Laboratory of Biochemistry, National Heart and Lung Institute. The press conference was sponsored by the Federation of American Scientists.

The Nobelists and the other scientists called for repeal of the National Cancer Act provision giving the President authority to appoint the NIH director. That provision, said the scientists, is a "major instrument" of political control over the research facility. Instead, they called on the President "to show his commitment to a politically independent" NIH by clearing his nominee for NIH chief with leading scientific societies.

And the Association of American Medical Colleges, in a letter to President Ford, urged him to name as the next NIH chief a medical scientist of international stature, with an understanding of biomedical research, and a background in government research administration. They put forward as their nominees Drs. J. Edward Rall, Scientific Director of the National Institute of Arthritis, Metabolism and Digestive Diseases, and Theodore Cooper, Deputy Assistant Secretary of Health, HEW.

A.A.M.C. Urges Separate Dept.

In an interview, Dr. John A. D. Cooper, A.A.M.C. president, noted that "The A.A.M.C. has pushed for a separate Department of Health. If we can't get that, then at the very least, the nation's top health officer should be a Deputy Secretary or Under Secretary, instead of Assistant Secretary for Health. That title would raise his status in the hierarchy and place him in a direct relationship with the Secretary [of HEW]."

Dr. Cooper suggested that Dr. Edwards has been "unhappy with the kind of influence he has had in H.E.W. and with the allocations of priorities and funding." N.H.

Cardiologists Honor Dr. Corday

Dr. Eliot Corday was recently honored by the American College of Cardiology, which dedicated a symposium to him and gave him an award. Left to right, Dr. Simon Dack, Dr. Corday, and Dr. Henry I. Russek.

'Excess' Prescriptions Cut by Data Feedback

Medical Tribune Report

CHICAGO—An information feedback loop in which the physician was given a monthly profile on his drug prescribing habits markedly reduced drug use in a study conducted at the Baltimore City Hospitals.

A drug prescribing index (DPI) was developed to measure usage, Dr. Michael W. Pozen of Johns Hopkins Hospital told the Association of American Medical Colleges here.

The DPI is essentially a ratio of the quantity of drug prescribed—expressed in 'ideal' units determined by the investigators in association with faculty members at Johns Hopkins School of Medicine—to the number of dosage days before the patient is next seen. A DPI of 3.0 would indicate that three times as much medication was prescribed as would have been appropriate for the interval. Johns Hopkins faculty considered a DPI of up to 1.5 to be reasonable.

During the first month of study, baseline DPIs were calculated for physicians in each of three clinics. Over the next 10 months, the experimental clinic was given a monthly prescribing profile. This report included the DPI for each prescription written and an explanation by the unit administor.

In the second clinic, the house physicians received an intensive faculty supervised educational program which included discussions of drugs, their indications, contraindications, and means for monitoring drug toxicity.

The third clinic was a traditional control group receiving no information.

Results showed that house officers in the first clinic quickly leveled off at about 1.4 in prescribing digoxin while the DPI of the other two clinics were 3.2 and 4.1, respectively. Similar results were seen in the data for methldopa and hydrochlorothiazide, the other two drugs involved in the study.

Special Neurologic Hospital

Medical Tribune World Service

TOKYO — The Tokyo Metropolitan Government will construct a 300-bed hospital in Fuchu to treat subacute myeloopticoneuropathy, Behçet's disease, and other intractable neurologic diseases. The hospital is to be completed by March 1977.

wine talk

By JOHN CHAMBERS
Author and Consultant to Morrell & Company, New York Wine Merchants

Sherry

Dr. Vincente Arrillaga, a Spanish physician whom I have known since my first visit to that country, passed through New York recently, and we had supper together. As usual, the conversation quickly turned to wine, and he remarked that of all the wines of the world, none has a more complex story than sherry, and yet no wine is taken so much for granted. He's right, of course, and hence this column on sherry.

The area around Jerez, in which sherry is produced, is hot and dry. The grapes ripen quickly and bake in the unrelenting sun, developing high sugar content. The two primary varieties grown around Jerez, the *palomino* and the *pedro jimenez*, have the merit of maintaining good acidity to balance this high sugar content. In Jerez the *palomino* is used for all dry sherries with the juice of the *pedro jimenez* being used as a sweetening agent, whereas in neighboring Montilla, the latter grape is used for both dry and sweet wines.

What Distinguishes Sherry

The key to sherry as we know it is a distinctive method of vinification and aging. Whereas contact with the air is avoided in the making of most wines, in the case of sherry it is sought, for air is needed to encourage the development of the *flor* yeast. As this yeast activates, it forms clusters or *flowers* that gradually coalesce into a thick scum, beneath which the yeast works at its traditional task of converting sugar to alcohol. Only when all the sugar left in the wine after fermentation has been converted, does the yeast settle to the bottom of the cask.

For the next few years the new wine is aged. Then when its quality has been definitely established, it is assigned to a *solera*. A *solera* is physically a stack of several wine casks, connected periodically by tubing, so that when wine is taken from the bottom cask, wine from the cask above will replace it, and so on in turn. It is into the top casks that the new wine will be poured.

The Stamp of the Past

Consequently, when you buy a sherry (or a madeira, since the same method is used) from a *solera* started in 1910, it means that there is probably an infinitesimal amount of that original sherry of 1910 in the bottle you purchase. However, and this is the key point, that original sherry has stamped the *solera* indelibly with its character, while the new wine added each year has maintained the freshness of the blend. The great complexity and depth of the finished product is the result.

Although sherrylike wines are made in many parts of the world, and many are good (particularly those of South Africa), none has the distinction of Spanish sherry. As Dr. Arrillaga puts it, there is only one Jerez, and that is in Spain!

Exceptionally well absorbed oral broad spectrum antibiotic may be taken with meals

Larocin™ (amoxicillin) achieves high blood and urine levels

Low incidence of diarrhea to date in clinical studies

NUTLEY, N.J.—Roche Laboratories recently introduced an oral broad spectrum antibiotic: Larocin (amoxicillin). Larocin represents a significant contribution to antibacterial chemotherapy, one which will perform effectively in the treatment of a wide range of infections due to susceptible organisms (see chart at right).

Absorption called the key

The key pharmacologic characteristic of Larocin (amoxicillin) is its rapid and efficient absorption from the gastrointestinal tract. Not only is it stable in stomach acid, but the presence of food has no significant effect on the antibiotic's absorption. Thus Larocin may be taken by patients on a convenient *t.i.d.* schedule without regard to meals. The reconstituted oral suspension and pediatric drops may be added to liquids such as formula, milk, fruit juice or soft drinks for easy administration to small children.

Because of its efficient absorption characteristics, high blood and urine levels of Larocin (amoxicillin) are rapidly achieved. Peak serum levels average 4.2 mcg/ml two hours after a single 250-mg oral dose and 7.5 mcg/ml one hour after a single 500-mg oral dose—both levels approximately twice as high as those obtained with equal doses of ampicillin.[1,2]

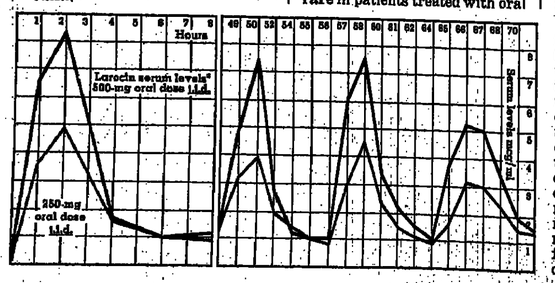
On a multiple-dose regimen, when given every eight hours for 3 days, the lowest mean serum levels of Larocin approximated 1.0 mcg/ml after 250 mg and 1.25 mcg/ml after 500 mg.[2] Although the therapeutic range of blood levels for the penicillins is not well established, these results demonstrate that blood levels may be expected to remain above the MIC's for all of the nonurinary pathogens susceptible to Larocin when it is administered at clinically recommended doses (see chart below).

Most of Larocin is excreted unchanged in the urine.[2] Average urinary excretion within 6 to 8 hours after oral administration ranges from 40 to 79% for the 250-mg dose and 59 to 79% for the 500-mg dose.[1-3]

1. Croydon EAP, Sutherland R: *Antimicrob Agents Chemother—1970*, pp. 427-430, 1971. 2. Neu HC, Winshell EB: *Antimicrob Agents Chemother—1970*, pp. 423-426, 1971. 3. Data on file, Hoffmann-La Roche Inc., Nutley, New Jersey. 4. Leigh DA: *Curr Med Res Opin 1*:10-18, 1972. 5. Bodey GP, Nance J: *Antimicrob Agents Chemother 1*:358-362, 1972.

Hypersensitivity reactions can occur

As with other penicillins, it is anticipated that adverse reactions to Larocin (amoxicillin) will be largely limited to sensitivity phenomena. While anaphylaxis is rare in patients treated with oral penicillins, the possibility must nevertheless be kept in mind. Larocin is contraindicated in patients with a history of penicillin hypersensitivity. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT. (See Warnings section of complete product information, a summary of which appears at right.)



GRAM-POSITIVE	
Alpha-hemolytic streptococci Beta-hemolytic streptococci *Streptococcus faecalis*	
Diplococcus pneumoniae	
Nonpenicillinase-producing staphylococci	
GRAM-NEGATIVE	
Hemophilus influenzae	
Escherichia coli	
Proteus mirabilis	
Neisseria gonorrhoeae	

In vitro bactericidal activity

Note: Because Larocin (amoxicillin) does not resist destruction by penicillinase, it is not effective against penicillinase-producing bacteria such as resistant staphylococci. All strains of Pseudomonas and most strains of Klebsiella and Enterobacter are resistant.

Otitis Media: The pathogens most commonly isolated were *Diplococcus pneumoniae* and *Hemophilus influenzae*. Of 130 cases with this diagnosis, 127 (98%) were rated as a "success" or "improvement" after treatment with Larocin (amoxicillin).

• • •

Streptococcal Sore Throat: A success rate of 86% (174 of 202 cases) was observed with Larocin against the responsible pathogen, beta-hemolytic streptococci.† The great majority of the 202 patients in this group were children who received the oral suspension.

• • •

Other Upper Respiratory Infections: Beta-hemolytic streptococci† were the offending organisms for most of the infections in this group, which were diagnosed primarily as pharyngitis, with some cases of tonsillitis and a few cases of sinusitis. A success rate of 82% (56 of 68 cases) was achieved with Larocin.

• • •

Lower Respiratory Infections: Treatment with Larocin resulted in "success" or "improvement" in all of the 52 cases in which *Diplococcus pneumoniae* was cultured. *Staphylococcus aureus* was also cultured in 26 of the 98 cases; Larocin showed "success" or "improvement" in 96% (25 of 26 cases). The most common clinical conditions were bronchitis and bronchopneumonia.

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Urinary Tract Infections: Cystitis, pyelonephritis and asymptomatic bacteriuria were the most frequent clinical diagnoses in this group. Of the 404 cases evaluated, *Escherichia coli* was cultured in 306 cases and treatment with Larocin resulted in "success" or "improvement" in 284 cases (93%). *Proteus mirabilis* was cultured in 70 patients, with Larocin effective in 67 (96%).

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Skin and Soft Tissue Infections: *Staphylococcus aureus* was cultured in 108 cases, with "success" or "improvement" in 104 (96%); while beta-hemolytic streptococci were cultured in 99 cases, with "success" in 97 (98%). Impetigo and abscess were the most frequent diagnoses.

• • •

Gonorrhea: Administered as a single 3-Gm oral dose, Larocin showed a success rate of 97% in both males (85 of 88 cases) and females (114 of 118 cases).

**Data on file, Hoffmann-La Roche Inc., Nutley, New Jersey 07110.*

†"Success" or "improvement" was determined by a combination of clinical and bacteriological criteria. In infections due to beta-hemolytic streptococci and N. gonorrhoeae, only successes were included.

Efficacy demonstrated in many infections

Amoxicillin has been administered successfully to patients with a wide range of commonly seen infections due to susceptible organisms.* Over-all clinical evaluation of amoxicillin therapy was considered a "success" or "improvement" in 1267 of 1350 evaluable cases (93.8%).†

Ages of the 1350 patients studied ranged from under one year to over 80 years. Larocin capsules were administered to 800 patients and oral suspension to the remaining 550. Dosage of the capsules ranged from 250 mg *t.i.d.* (the most frequently used dosage) to a single 3-Gm dose for the treatment of acute uncomplicated gonorrhea. Dosage of the oral suspension ranged from 50 mg *t.i.d.* to 250 mg *t.i.d.*, with 125 mg *t.i.d.* the most frequent. The majority of patients were treated from seven to 10 days. A breakdown by type of infection follows:

Low incidence of side effects reported to date

During the clinical investigations with amoxicillin, all cases treated were evaluated for side effects. No side effects or laboratory abnormalities which would be considered unusual for a penicillin derivative were reported by any of the investigators.

In 2658 total courses of therapy with amoxicillin, therapy was discontinued in only 52 patients (1.9%) because of drug-related side effects. Laboratory abnormalities possibly related to amoxicillin occurred infrequently.

In these studies, there was a low incidence of diarrhea reported with amoxicillin capsules—1.7% or 30 of 1811 patients. Especially noteworthy was the low incidence of diarrhea reported with amoxicillin oral suspension—only 2.8% or 24 of 847 patients, significantly less ($p<0.05$) than the incidence of diarrhea with ampicillin oral suspension (5.8% or 15 of 282 patients).

In breaking down the over-all incidence of diarrhea by age groups, it was found that in the group from 0 to 1 (newborn and 1-year-old infants), 18 of 108 patients receiving amoxicillin oral suspension developed diarrhea, for an incidence of 12%. This represents over one-half the total number of diarrhea cases seen in the 847 patients treated with amoxicillin oral suspension.

Throughout each of the remaining age categories, starting from age 2 to 10 and in the general grouping from age 11 to 20, the incidence of diarrhea in patients treated with amoxicillin oral suspension ranges from 2% down to 0 in the older groups. There were few cases of diarrhea beyond the age of six.

The incidence of diarrhea with Larocin (amoxicillin) can therefore be expected to be considerably higher in the newborn and infant age groups than in older children, which is true of all antibiotics.

Drug-Related Side Effects Associated with Amoxicillin

Based upon 2658 courses of therapy: 1811 with the capsules and 847 with the oral suspension.

SIDE EFFECT	CAPSULES #	CAPSULES %	SUSPENSION #	SUSPENSION %
Diarrhea	24	1.3	18	2.1
Rash	24	1.3	17	2.0
Nausea	7	0.3	1	0.1
Urticaria	8	0.4	2	0.2
Moniliasis	7	0.3		
Nausea/Vomiting	4	0.2		
Diarrhea/Nausea	3	0.1		
Vomiting	2	0.1	4	0.4
Dizziness	2	0.1		
Colitis	2	0.1		
Nausea/Headache	2	0.1		
Rash/Urticaria	2	0.1	1	0.1
Esophageal Spasm	1	0.05		
Stomachache	1	0.05	1	0.1
Belching	1	0.05		
Drowsiness	1	0.05		
Belching/Numbness/Tingling/Itching	1	0.05		
Fever/Itching	1	0.05		
Difficult Breathing	1	0.05		
Mucus in Pharynx	1	0.05		
Diarrhea/Urticaria	1	0.05		
Diarrhea/Vomiting	1	0.05	4	0.4
Dizziness/Headache	1	0.05		
Conjunctival Ecchymosis	1	0.05		
G.I. Bleeding	1	0.05		
Abdominal Cramps	1	0.05		
Diarrhea/Rash	1	0.05	1	0.1
Rash/Diarrhea/Vomiting			1	0.1
Sore Tongue			1	0.1
Rash/Vomiting			1	0.1
TOTAL	102	5.6	52	6.1

Usual Adult and Pediatric Dosages

INDICATION	STRAIN ISOLATED	ADULT DOSAGE	PEDIATRIC DOSAGE*
Infections of the ear, nose, throat	Streptococci, pneumococci, nonpenicillinase-producing staphylococci, *H. influenzae*	250 mg t.i.d.	Oral Suspension: 20 mg/kg/day in divided doses t.i.d. Drops: Under 6 kg (13 lbs): 0.5 ml t.i.d.; 6-8 kg (13-18 lbs): 1 ml t.i.d.
Infections of the lower respiratory tract	Streptococci, pneumococci, nonpenicillinase-producing staphylococci, *H. influenzae*	500 mg t.i.d.	Oral Suspension: 40 mg/kg/day in divided doses t.i.d. Drops: Under 6 kg (13 lbs): 1 ml t.i.d.; 6-8 kg (13-18 lbs): 2 ml t.i.d.
Infections of the genito-urinary tract	*E. coli*, *Proteus mirabilis*, *Strep. faecalis*	250 mg t.i.d.	Oral Suspension: 20 mg/kg/day in divided doses t.i.d. Drops: Under 6 kg (13 lbs): 0.5 ml t.i.d.; 6-8 kg (13-18 lbs): 1 ml t.i.d.
Infections of the skin and soft tissues	Streptococci, susceptible staphylococci and *E. coli*	250 mg t.i.d.	Oral Suspension: 20 mg/kg/day in divided doses t.i.d. Drops: Under 6 kg (13 lbs): 0.5 ml t.i.d.; 6-8 kg (13-18 lbs): 1 ml t.i.d.
Severe infections, or infections caused by less susceptible organisms		500 mg t.i.d.	Oral Suspension: 40 mg/kg/day in divided doses t.i.d.
Gonorrhea, acute uncomplicated anogenital and urethral infections (males and females)	*N. gonorrhoeae*	3 grams—single oral dose	

*Note: Children weighing more than 8 kg (18 lbs) should receive the appropriate dose of the Oral Suspension: 125 mg or 250 mg/5 ml. Children weighing more than 20 kg should be dosed according to adult recommendations.

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Infections due to susceptible strains of the following gram-negative organisms: *H. influenzae, E. coli, P. mirabilis* and *N. gonorrhoeae*; and gram-positive organisms: streptococci (including *Streptococcus faecalis*), *D. pneumoniae* and nonpenicillinase-producing staphylococci. Therapy may be instituted prior to obtaining results from bacteriological and susceptibility studies to determine causative organisms and susceptibility to amoxicillin.

Contraindications: In individuals with history of allergic reaction to penicillins.

WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH MORE FREQUENT FOLLOWING PARENTERAL THERAPY, ANAPHYLAXIS HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. MORE LIKELY IN INDIVIDUALS WITH HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. BEFORE THERAPY, INQUIRE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF ALLERGIC REACTION OCCURS, INSTITUTE APPROPRIATE THERAPY AND CONSIDER DISCONTINUANCE OF AMOXICILLIN. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, ADMINISTER OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, AS INDICATED.

Usage in Pregnancy: Safety in pregnancy not established.

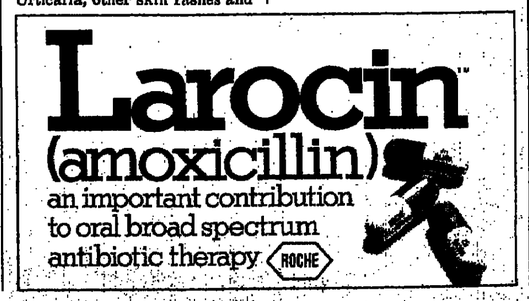
Precautions: As with any potent drug, assess renal, hepatic and hematopoietic function periodically during prolonged therapy. Keep in mind possibility of superinfections with mycotic or bacterial pathogens; if they occur, discontinue drug and/or institute appropriate therapy.

Adverse Reactions: As with other penicillins, untoward reactions will likely be essentially limited to sensitivity phenomena and more likely occur in individuals previously demonstrating penicillin hypersensitivity and those with history of allergy, asthma, hay fever or urticaria. Adverse reactions reported as associated with use of penicillins: *Gastrointestinal:* Nausea, vomiting, diarrhea. *Hypersensitivity Reactions:* Erythematous maculopapular rashes, urticaria. *NOTE:* Urticaria, other skin rashes and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Discontinue amoxicillin unless condition is believed to be life-threatening and amenable only to amoxicillin therapy. *Liver:* Moderate rise in SGOT noted, but significance unknown. *Hemic and Lymphatic Systems:* Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, agranulocytosis. All are usually reversible on discontinuation of therapy and believed to be hypersensitivity phenomena.

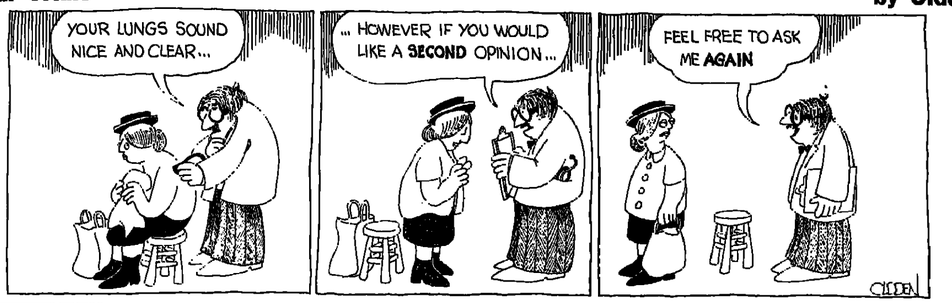
Dosage: *Ear, nose, throat, genitourinary tract, skin and soft tissue infections*—Adults: 250 mg every 8 hours. Children: 20 mg/kg/day in divided doses every 8 hours; under 6 kg, 0.5 ml of Pediatric Drops every 8 hours; 6-8 kg, 1 ml of Pediatric Drops every 8 hours. *Lower respiratory tract infections and severe infections or those caused by less susceptible organisms*—Adults: 500 mg every 8 hours. Children: 40 mg/kg/day in divided doses every 8 hours; under 6 kg, 1 ml of Pediatric Drops every 8 hours; 6-8 kg, 2 ml of Pediatric Drops every 8 hours. *Gonorrhea* (acute uncomplicated anogenital and urethral infections)—Males and females: 3 grams as a single oral dose. NOTE: Children weighing more than 8 kg should receive appropriate dose of oral suspension 125 mg or 250 mg/5 ml. Children weighing 20 kg or more should be dosed according to adult recommendations.

Note: In gohorrhea with suspected lesion of syphilis, perform dark-field examinations before amoxicillin therapy and monthly serological tests for at least four months. In chronic urinary tract infections, frequent bacteriological and clinical appraisals are necessary. Smaller than recommended doses should not be used. In stubborn infections, several weeks' therapy may be required. Except for gonorrhea, continue treatment for a minimum of 48-72 hours after patient is asymptomatic or bacterial eradication is evidenced. Treat hemolytic streptococcal infections for at least 10 days to prevent acute rheumatic fever or glomerulonephritis.

Supplied: Amoxicillin as the trihydrate: Capsules, 250 mg and 500 mg; oral suspension, 125 mg/5 ml and 250 mg/5 ml; pediatric drops, 50 mg/ml.



Clinical Trials **by Oldden**



TRIBUNE SPORTS REPORT

Blind Swiss Physiotherapist Developed Skiing for Blind

Medical Tribune World Service

GENEVA—A blind physiotherapist can take much of the credit for the fact that skiing has become a sport that can be enjoyed by the blind.

Roger Allemand lost his sight as a result of an accident during military service when he was 21. In 1969 he founded the *Groupement Romand des Skieurs Aveugles* (G.R.S.A.—Organization for Blind Skiers in French Switzerland).

"To begin with I was president, secretary, treasurer—everything in one," he said.

Now his techniques are being studied in other countries, including the United States.

The G.R.S.A. has some 25 blind or partially sighted members and a panel of 50 instructors. With some financial help from the Swiss Government it arranges instruction and runs several group meetings and activities, including an annual camp lasting one week.

Exacting Course for Instructors

All the instructors are certified by the Swiss Ski School and have taken a special two-day course in instructing the blind. According to one newly qualified instructor, the course is "very exacting, requiring great powers of concentration."

The G.R.S.A. method stresses safety. Both pupil and instructor wear special parkas—yellow with a black band for the blind pupil and red with a black band for the instructor, both with the distinctive badge of the organization on the left sleeve. The instructor keeps about 1 M. behind his pupil and guides him every few seconds with verbal instructions, based to some extent on the principles used in aviation.

"Pierre, forward 10 o'clock" indicates to the skier, who is assumed to be facing 12 o'clock, the direction he must take.

Before he puts on a ski, however, he must undergo some physical preparation. The G.R.S.A. holds an autumn meeting at which all new members receive instructions in this regard and are given a cassette describing simple exercises. During the season they ski on average once a week.

Blind people learn fast, Mr. Allemand said. Not having the distractions of sight, they concentrate their attention on the words of the instructor. Denied the use of their eyes as a balancing aid, they develop a sense of balance that allows them to adapt to the changes in terrain, quality of snow, and other factors.

He demonstrated this for MEDICAL TRIBUNE by jumping lightly onto a large beach ball and balancing on it for several minutes.

Mr. Allemand and a 26-year old woman pupil recently made a long descent with their instructors down the Rosa Blanche snowfields. He and an instructor took part in the Nordic ski marathon in the St. Moritz region in 1973, covering 42 Km. in five hours.

Mr. Allemand is particularly proud of the fact that since its foundation no member of the G.R.S.A. has had a serious accident.

Medicine on Stamps

Joseph Kerwin

The first American physician to go into space studied medicine at Northwestern University, receiving his M.D. in 1957. While serving his internship at General Hospital, Washington, he became a flight surgeon with the Marines. In 1965 he was selected for astronaut training by NASA. He became a scientist-pilot for Skylab in 1973 and spent 28 days in space.

Text: Dr. Joseph Klar
Stamps: Minkus Publications, Inc., New York

Neuroleptic Analgesia Is Used in France In Open Heart Surgery With Good Results

Medical Tribune World Service

MEXICO CITY—Good results with neuroleptic analgesia in open heart surgery were reported by a French anesthesiologist in 2,000 patients. Droperidol was used in association with phenoperidine in 1,900 operations and with fentanyl in 100. The combinations were found to be satisfactory in maintaining stability of cardiac output with a lowering of peripheral vascular resistances, and particularly favorable in coronary artery surgery.

Experience in some 8,000 open heart operations at the Faculté Broussais Hôtel Dieu, Université de Paris, was described by Dr. Jean Claude Salamagne, Professor of Anesthesiology, to the First International Congress of Anesthesiology here.

Dr. Salamagne presented preliminary findings of recent work with the administration of a muscle relaxant, pancuronium, prior to induction of analgesia at high dosage. A mild dose of diazepam or thiopental sodium was given before the pancuronium for patient comfort. No definitive conclusions could be presented because of the limited number of cases so far, but the general impression, Dr. Salamagne said, was that it may be a useful procedure.

High dosages of fentanyl were found to produce persistent deep respiratory depression, lasting three or four hours after the final injection, which required respiratory assistance. This was not considered important, however, since the patient benefits for several hours from the residual sedation.

Drop In Pension Values Protested by WHO Staff

Medical Tribune World Service

GENEVA—The World Health Organization staff, which include about 500 physicians, held a brief stoppage at the headquarters building here in protest over the declining value of their prospective pensions. Officials of the W.H.O. staff association said that pension values have dropped some 30 per cent since 1971 as a result of devaluation of the U.S. dollar, and the revaluation of some other currencies, including the Swiss franc.

All professional-grade staff of United Nations organizations in Europe are paid in U.S. dollars.

IMMATERIA MEDICA

By DUDLEY STRAUS

Odds and Ends

• Seekers of a Cause, or Romanian patriots, may be interested in the following letter to the editor of *Lancet:*

"BABES OR PETRI DISH?

"SIR,—In his first treatise on bacteriology, published in May, 1885, Victor Babes described the use of a low-walled jar for bacteria isolations. In the same year Nicati and Rietsch also mentioned these jars, which they used for the isolation of the cholera vibrio. In 1887 Petri described his use, on a large scale, of this type of low-walled jar, which became known as the Petri-Schalen or Petri dish. Later, Fränkel supported Babe's assertion that the credit for the conception and application of this idea should go to Babes and not to Petri. Is it now too late to try to claim this discovery for Romania?

Stefan S. Nicolau Institute of Virology,
285 Sos. Mihai Bravu,
Bucharest, Romania.
VINCENT T. BABES."

We confess we were attracted to it by our failure to recognize the correct meaning of "Babes"

• Anyone in New York on January 17 might be interested in the Scientific Program being presented by the New York Center for Psychoanalytic Training:

"Dr. Benjamin Brody: *The Sexual Meaning of the Axillae (Armpits).*"

• Mephitiphobes may be interested to learn that two scientists from the University of New Hampshire have determined that the wrong chemical has been blamed for the offensive odor produced by skunks. (You maybe wondered what a mephiti- was?)

The guilty ingredients turn out to be crotyl mercaptan, isopentyl mercaptan, and methyl crotyl disulphide, and *not* innocent and wrongly accused *n*-butyl mercaptan.

• "WASHINGTON (UPI)—The Agriculture Department today announced a price support program for the 1974 crop of tung nuts, but officials noted quickly that farmers probably will not harvest any tung nuts this year."

And that's the way it goes, these days.